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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,734	11/21/2003	Solomon S. Steiner	1951300.00060	3538

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EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	PAPER NUMBER
1616	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,734	STEINER ET AL.	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33 and 35-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33 and 35-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/23/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 33 and 35-44 are pending. The notice of allowance mailed on February 13, 2009 appears to have crossed in time, regarding the time the allowance was sent to the mailroom and the time the Information Disclosure Statement submitted on January 23, 2009 was added to the electronic file for the Examiner's review. Upon review of the references cited on the 1/23/09 IDS new rejections were determined to be necessary, as set forth below. The application is hereby withdrawn from allowance, the allowance mailed on February 13, 2009 is hereby vacated, and prosecution is reopened.

Claim Objections

Claim 41 is objected to because of the following informalities: the commas on line 2 of claim 41 after the word "with" and before the words "the patient" are unnecessary, because the commas do not separate a series of alternative administration times, wherein a series constitutes three or more items. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 33 and 34-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 33 is indefinite and confusing because in the product-by-process steps it makes reference to "microparticles of diketopiperazine," however, the remainder of the claim refers explicitly to "a diketopiperazine derivative." Thus, it is unclear from the internal claim inconsistency whether the diketopiperazine derivative described in most of claim 33 is the same as the diketopiperazine described in the product by process steps.

The remaining claims are rejected as depending from a rejected claim.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 33 and 35-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Steiner et al. (WO 96/3614) (new IDS reference).

Applicants claim a method of delivering monomeric or dimeric insulin comprising administering to a patient a formulation comprising an effective amount of insulin complexed with a diketopiperazine derivative having the formula 2,5-diketo-3,6-di(4-X-aminobutyl)piperazine, wherein X is selected from the group consisting of fumaryl, succinyl, maleyl, and glutaryl.

Steiner discloses a method of delivering a drug to the pulmonary system comprising administering to a patient in need of treatment an effective amount of microparticles incorporating a therapeutic agent (i.e. insulin) (Steiner claim 11), wherein the microparticles have a diameter between 0.5 microns and 10 microns and the microparticles are made from diketopiperazines (Steiner claims 8-9). **Steiner discloses a specific suitable diketopiperazine as being 2,5-diketo-3,6-di(4-succinyl-**

aminobutyl)piperazine, which is one of the specific diketopiperazine materials explicitly recited in Applicants' claims. Steiner generally describes suitable diketopiperazines for the formation of microparticles from page 6, line 5 through page 7, line 26. Suitable acidic side-groups for the diketopiperazine are disclosed from page 6, line through page 7, line 3, and include fumaryl, succinyl, maleyl, and glutaryl diketopiperazines. **Fumaryl diketopiperazine is indicated as being the preferred diketopiperazine** (pg. 7, lines 25-26). The diketopiperazine microparticles are prepared according to the process described on pg. 13, line 30 through pg. 14, line 3 of Steiner and utilize a bicarbonate solution. It is the Examiner's position that the process described on pages 13-14 of Steiner inherently includes a suspension of diketopiperazine particles, because the solution described on page 13 is not described as being clear and thus could reasonably include suspended microparticles. **The microparticles are most preferably stored in a lyophilized form** (i.e. as a lyophilized powder) (pg. 17, lines 6-8 and 18, lines 1-5). It is the Examiner's position that an ordinary skilled artisan could envisage the claimed method of instant claims 33 and 36, wherein the diketopiperazine microparticles are made from either 2,5-diketo-3,6-di(4-succinyl-aminobutyl)piperazine or alternatively, 2,5-diketo-3,6-di(4-fumaryl-aminobutyl)piperazine, the therapeutic agent is insulin, and the insulin is inherently complexed to said microparticles.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 37-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Steiner et al. (WO 96/3614) (new IDS reference) in view of Edelman, S.V. (*Abstract only* of: "Type II Diabetes Mellitus," Advances in Internal Medicine, 1998, 43, pp 449-500).

Applicant Claims

Applicants claim a method as described above, wherein in some embodiments the diketopiperazine has X that is maleyl or glutaryl, and in other embodiments the method requires administration to a patient with Type II diabetes concurrently or less than 20 minutes prior to the patient eating a meal. In another claimed embodiment the dose of the insulin given is indicated as being equivalent to about 6 IU of insulin.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Steiner have been set forth above. The teachings of Edelman were set forth in the office action mailed May 12, 2006 and are restated herein below.

Edelman teaches that when combination therapy fails, a split-mixed regimen using premixed 70/30 insulin pre-breakfast and pre-dinner **can be effective in obese patients with Type II diabetes** (abstract).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Steiner lacks the teaching of (i) treating a patient with Type II diabetes, (ii) wherein treatment occurs concurrently with or less than 20 minutes prior to the patient eating a meal, and (iii) wherein the composition delivered to the patient has a dosage of 6 IU of insulin, provided in one or more unit doses. This deficiency is cured by the teachings of Edelman. Steiner does not anticipate claims 37-38, because Steiner does not exemplify maleyl or glutaryl diketopiperazine microparticles. Nonetheless, Steiner does suggest maleyl or glutaryl diketopiperazine microparticles.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to a person of ordinary skill in the art to modify the teachings of Steiner with the teachings of Edelman, because Edelman teaches that insulin may be used to treat obese patients with Type II diabetes, when combination therapy fails and insulin is a well-known therapeutic agent for the treatment of diabetes (Edelman). A skilled artisan would have been further motivated to combine the teachings of Steiner and Edelman and would have had a reasonable expectation of success upon combination, because Edelman teaches that the treatment of obese patients with insulin, when combination therapy fails, can be very effective. Regarding the concentration of insulin delivered upon administration, the amount of a specific ingredient (e.g. the dosage of an active agent) in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of applicant's invention.

Regarding the selection of maleyl or glutaryl diketopiperazine microparticles, although these are not exemplified by Steiner these are suggested. See page 6, line 25 through page 7, line 2. See also page 14, lines 30-32, wherein the method for making microparticles with diketopiperazines is described as using a diketopiperazine with acidic side chains. Applicants' declaration data submitted on October 9, 2007 is noted, but does

not overcome the instant rejection because it is not a proper side-by-side comparison with the closest prior art (i.e. Steiner). Specifically, the declaration compares diketopiperazine/insulin microparticles prepared by dissolution of the diketopiperazine in liquid ammonia. The instant reference utilizes bicarbonate, thus, the method of making used in the comparison microparticles cited in the declaration are different and are not commensurate in scope with the Steiner's teachings. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 33 and 35-39 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-7, and 10-14 of U.S. Patent No. 6,071,497 (USPN '497) (WO 96/3614) (new IDS reference). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are substantially overlapping and scope and mutually obvious. Both the cited claims of the instant application and those of UPSN '497 recite methods of delivering insulin, comprising the administration of diketopiperazine microparticles further comprising insulin. Both USPN '497 and the instant application recite a method wherein the composition is in the form of a dry powder (claim 39 of the instant application and claim 6 of USPN '497). Although the cited claims of USPN '497 do not recite that the insulin is complexed to the diketopiperazine, it would have been apparent that this associative interaction is a property of a composition comprising both a diketopiperazine and insulin. The cited claims of USPN '497 do not recite specific diketopiperazine derivatives, such as fumaryl diketopiperazine; however, the term "diketopiperazine" is understood to refer to a genus of compounds, which encompasses fumaryl diketopiperazine and other amidated diketopiperazines (e.g. succinyl, maleyl, glutaryl, etc.). The cited claims of USPN '497 do not recite a method of making the diketopiperazine/insulin microparticles. The teachings of Steiner set forth above are provided to cure this deficiency. It is the Examiner's position that the diketopiperazine microparticles made according to Steiner's method necessarily contain complexed insulin. Therefore, claims 33 and 35-39 are *prima facie* obvious over claims 1, 4-7, and 10-14 of U.S. Patent No. 6,071,497.

Claims 33 and 35-39 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-7, and 10-12 of U.S. Patent No. 6,428,771 (USPN '771) (WO 96/3614) (new IDS reference). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are substantially overlapping and scope and mutually obvious. Both the cited claims of the instant application and those of UPSN '771 recite methods of delivering insulin, comprising the administration of diketopiperazine microparticles further comprising insulin. Both USPN '771 and the instant application recite a method wherein the composition is in the form of a dry powder (claim 39 of the instant application and claims 6 and 12 of USPN '771). Although the cited claims of USPN '771 do not recite that the insulin is complexed to the diketopiperazine, it would have been apparent that this associative interaction is a property of a composition comprising both a diketopiperazine and insulin. The cited claims of USPN '771 do not recite specific diketopiperazine derivatives, such as fumaryl diketopiperazine; however, the term "diketopiperazine" is understood to refer to a genus of compounds, which encompasses fumaryl diketopiperazine and other amidated diketopiperazines (e.g. succinyl, maleyl, glutaryl, etc.). The cited claims of USPN '771 do not specify a method of making the diketopiperazine microparticles. The teachings of Steiner set forth above are provided to cure this deficiency. It is the Examiner's position that the diketopiperazine microparticles made according to Steiner's method necessarily contain complexed insulin. Therefore, claims 33 and 35-39 are *prima facie* obvious over claims 1, 4-7, and 10-12 of U.S. Patent No. 6,428,771.

Claims 33-39 and 42 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 23-36 of copending Application No. 10/706,243 (copending '243) (WO 96/3614) (new IDS reference). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are substantially overlapping in scope and mutually obvious. Both claims sets recite methods of delivering diketopiperazine microparticles selected from a group consisting of succinyl, glutaryl, malelyl, and fumaryl diketopiperazine, wherein the composition is administered to the lungs of a patient in need. Steiner is provided for the teaching of a method of making diketopiperazine/insulin microparticles, wherein the insulin is complexed (insulin is necessarily complexed). Although the claims of copending '243 do not recite a composition in a dry powder form, it would have been obvious to a person of ordinary skill in the art at the time of the instant invention that a powder is a particulate composition, and would be rendered obvious by a composition comprising microparticles. Regarding the amount of insulin present in a given composition utilized in the practice of the method of both applications, the amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of applicant's invention. The claims of copending '243 do not recite any product-by-process limitations for the making

of diketopiperazine/insulin microparticles. The teachings of Steiner set forth above are provided to cure this deficiency. It is the Examiner's position that the diketopiperazine microparticles made according to Steiner's method necessarily contain complexed insulin. Therefore, claims 33-39 and 42 are *prima facie* obvious over claims 23-36 of copending application '243.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 33, 35, and 40-42 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 and 17-23 of copending Application No. 11/329,686 (copending '686) (WO 96/3614) (new IDS reference). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are substantially overlapping in scope and are mutually obvious. Both claim sets recite methods of delivering insulin to a patient in need thereof. The term "exogenously administered" reads on the term "delivery." Both methods also recite the limitation that the patient is a Type II diabetic (claim 5 of copending '686 and claim 40 of the instant application). Claims 17-23 of copending '686 recite a method wherein ***the composition comprises a complex*** between a diketopiperazine (e.g. fumaryl diketopiperazine) and insulin. It would have been apparent to a skilled artisan that inhalation of the composition recited in the method claims of copending '686 would result in delivery of said composition to the lungs of a patient in need thereof. Therefore, claims 33, 35 and 40-42 are *prima facie* obvious over claims 1-5 and 17-23 of copending Application No. 11/329,686 (copending '686).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Claims 33 and 35-44 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner is on a flexible schedule, but can normally be reached on M-F ~10am~5:30 pm, and Saturdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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